

**CAPSULE PREPARATION AND IT PRODUCTION****Publication number:** JP2000239159**2000- 239 159****Publication date:** 2000-09-05**Inventor:** MORI TAKAHARU; ITO SATOMUNE; SANO  
YASUHIKO; ITO MAKOTO; ENOMOTO ITSUMI**Applicant:** NITTO YAKUHIN KOGYO KK; TOKAI CAPSULE KK**Classification:****- International:** A23P1/04; A61J3/07; A61K9/48; A23P1/04; A61J3/07;  
A61K9/48; (IPC1-7): A61K9/48; A23P1/04; A61J3/07**- European:****Application number:** JP19990041579 19990219**Priority number(s):** JP19990041579 19990219**Report a data error here****Abstract of JP2000239159**

**PROBLEM TO BE SOLVED:** To obtain a capsule preparation characteristic in that a medicament packed in the capsule contains at least two kinds of medicinal ingredients which are separated into a plurality of ingredient phases, and by making the separated state visibly recognizable from the outside of the capsule by a relevant person to be administered, the person can easily recognize that this capsule preparation contains a plurality of the medicinal ingredients therein and has high therapeutic efficacy, and to provide a method for producing the capsule preparation. **SOLUTION:** This capsule preparation is made up of a capsule and a medicament packed therein, wherein it is characterized by that the medicament is separated into a plurality of ingredient phases, the separated state is visibly recognizable from the outside of the capsule preparation, and at least one of these ingredient phases is in a liquid state.

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**CLAIMS**

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**[Claim(s)]**

[Claim 1] The capsule characterized by any one component phase being in a liquid condition at least among these component phases while these drugs have separated into two or more component phases and this separation condition can check by looking from the capsule exterior in the capsule which consists of drugs with which it filled up in the capsule and this capsule.

[Claim 2] The capsule according to claim 1 each component phase of whose is in a liquid condition.

[Claim 3] The capsule according to claim 1 or 2 which drugs have separated in the shape of a layer for every component phase.

[Claim 4] The capsule according to claim 1 from which it has two or more kinds of component phases which are in the liquid condition at least, and the component phases of these liquid condition are separating the letter of emulsion.

[Claim 5] The capsule according to claim 1 from which the component phase used as the component phase which is equipped with the component phase which is in the liquid condition, and the component phase used as a solid state at least, and is in these liquid condition, and a solid state is separating the letter of suspension.

[Claim 6] A capsule given in any of claim 1 equipped with the component phase which consists of a hydrophilic liquid, and the component phase which consists of a hydrophobic liquid thru/or claim 5 they are.

[Claim 7] A capsule given in any of claim 1 currently classified by color for every component thru/or claim 7 they are.

[Claim 8] How to manufacture the capsule according to claim 1 which includes the process filled up with the drugs with which any one component phase is in the liquid condition at least among said component phases in a capsule so that the check by looking of the condition of having separated into said two or more component phases may be attained from the outside of a capsule while separating into two or more component phases.

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**DETAILED DESCRIPTION**

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**[Detailed Description of the Invention]****[0001]**

[Field of the Invention] This invention can check by looking from the capsule exterior that the drugs with which the interior of a capsule is filled up have separated into the detail more about a capsule and its manufacture approach, and relates to the capsule which can be made by this to recognize that therapeutic effectiveness is a high capsule also to the recipe person of a capsule, and its manufacture approach.

**[0002]**

[Description of the Prior Art] Conventionally, various capsules are sold and there is a capsule which comes to fill up the drugs which consist only of a component phase of a liquid condition in it. The capsule which is the outer shell is colored, and since it is opaque, the conventional capsule filled up with such drugs cannot see internal drugs in many cases, and it cannot imagine [ whether the capsule is filled up with the drugs which consist of a component phase of the liquid condition containing what kind of drug effect component, and ] them easily for a recipe person.

[0003] Therefore, the capsule which can be checked by looking from the capsule outside is developed [ drugs / transparency or / with which presupposed that it is translucent and the interior was filled up ] in the capsule. However, in such a capsule, even if it is the case where two or more kinds of drug effect components are contained as drugs, after these drugs have dissociated, it does not necessarily fill up, and is in the condition of having been mixed with homogeneity.

[0004] Therefore, when the recipe person of a capsule observes internal drugs from the capsule exterior, it does not understand [ how many kinds of drug effect components are contained in drugs, and ]. For this reason, it thinks that the therapeutic effectiveness of the capsule concerned of a recipe person is low, and taking combining various chemicals in addition to the capsule concerned is also considered.

However, in this way, when it takes combining various chemicals, there is a possibility of producing an incompatibility and it is dangerous on the contrary.

**[0005]**

[Problem(s) to be Solved by the Invention] The place which it is made in order that this invention may solve the above-mentioned technical problem, and is made into the purpose When the drugs with which the interior of a capsule is filled up contain two or more kinds of drug effect components, while these drug effect components separate into two or more component phases The recipe person of this capsule is received by enabling the capsule exterior to the check by looking of this condition of having dissociated. This capsule contains two or more kinds of drug effect components inside, and is to offer the capsule which is easy to make it recognize that it is a capsule with high therapeutic effectiveness, and its manufacture approach.

**[0006]**

[Means for Solving the Problem] In the capsule which consists of drugs with which it filled up in the capsule and this capsule , it is characterize by any one component phase be in a liquid condition at least among these component phases while these drugs have separate into two or more component phases and

a separation condition can check by looking the capsule concerning this invention which solves the above-mentioned technical problem from the capsule exterior.

[0007] It does not matter even if it is the hard thing currently called the hard filled capsule even if the well-known thing currently used conventionally is usable and is an elastic thing currently called the soft capsule as a capsule in the above-mentioned configuration. However, when a hard filled capsule is used, it is required to carry out a seal firmly so that the drugs containing the liquid component with which it was filled up in the capsule may not leak out of a capsule.

[0008] Moreover, as for the drugs with which it is filled up in a capsule, it is desirable that each two or more component phases which constitute these drugs are in a liquid condition, and it is more desirable to have dissociated in the shape of a layer for every component phase in this case. While it be desirable to make it separate into two or more component phases using the difference in the property of this component phase and being fastidious including the component phase which consists of a hydrophilic liquid at least, and the component phase which consists of a hydrophobic liquid, it replaces with this, and two or more component phases are the difference of the consistency of each drug solution, respectively 0.001 g/cm<sup>3</sup>. It is desirable to consider as the above and to also make drugs divide into two or more component phases.

[0009] Moreover, it may be made to classify by color for every component phase. Although it is desirable to use the color of the drug effect component itself as for classification by color, it may be made to classify by color by adding the coloring agent which does not check drug effect to each component phase if needed. The above capsules may be manufactured by being filled up with the drugs with which any one component phase is in the liquid condition at least among said component phases in a capsule so that the check by looking of the condition of having separated into said two or more component phases may be attained from the outside of a capsule while separating into two or more component phases.

[0010] The capsule concerning this invention which solves the above-mentioned technical problem may be carrying out the configuration characterized by the ability of the condition of not only the gestalt separated in the shape of a layer but drugs having contained the hydrophilic liquid and the hydrophobic liquid, and this hydrophilic liquid and this hydrophobic liquid having dissociated in the shape of emulsion, and having dissociated in the shape of [ this ] emulsion to check by looking from the capsule exterior.

[0011] Moreover, the capsule concerning this invention which solves the above-mentioned technical problem may be carrying out the configuration characterized by the ability of the condition contained the component phase used as the component phase from which drugs are in the liquid condition, and a solid state, and the component phase used as the component phase which is in these liquid condition, and a solid state had dissociated in the shape of suspension, and dissociated in the shape of [ this ] suspension to be able to check by looking from the capsule exterior.

[0012] In addition, in the above-mentioned configuration, with a component phase, you could be formed only from the drug effect component with which a capsule is filled up, and the drug effect component was dissolved in the solvent, and it could be formed, and is not especially limited.

[0013]

[Embodiment of the Invention] Hereafter, the gestalt of 1 operation of this invention is explained to a detail. Even if there are few two or more component phases, the drugs with which the interior of the capsule in the gestalt of this operation is filled up have any one component phase in a liquid condition, while having separated into two or more component phases within a capsule.

[0014] In the case of the component phase in a liquid condition, as long as it is the liquid which does not dissolve a capsule as a solvent which dissolves a drug effect component, even if it is which liquid, it can use regardless of whether it is a hydrophilic property or it is hydrophobicity. As a hydrophilic liquid, polyhydric alcohol, such as lower alcohol, such as ethanol, a glycerol, glycetyl triacetate, ethylene glycol, propylene glycol, a polyethylene glycol, and a polypropylene glycol, isomerization honeydew, the liquid surfactant of a hydrophilic property, the thing that combined these are mentioned, for example.

[0015] On the other hand, as a hydrophobic liquid, triglycerides, such as a medium-chain-fatty-acid triglyceride, corn oil, olive oil, safflower oil, cotton seed oil, sesame oil, soybean oil, oleum rapae, peanut oil, palm oil, sunflower oil, jojoba oil, the poppy oil, a liquid paraffin, an oleophilic oily surfactant, the thing that combined these are mentioned.

[0016] Moreover, especially as a drug effect component which dissolves in a hydrophilic liquid, although not limited, a benzalkonium chloride, water soluble vitamin, an antipyrin, chlorpromazine hydrochloride, diphenhydramine hydrochloride, naphazoline hydrochloride, guaifenesin, sodium salicylate, dextromethorphan hydrobromide, chlorpheniramine maleate, acetaminophen, caffeine, dl-methylephedrine hydrochloride, dihydrocodeine phosphate, diprophylline, etc. are mentioned, for example.

[0017] On the other hand, especially as a drug effect component which dissolves in a hydrophobic liquid, although not limited, camphor, fat soluble vitamin, liver oil, a borneol, metenolone acetate, ibuprofen, isopropylantipyrine, ethenzamide, etc. are mentioned, for example. Moreover, you may make it add to each component phase, respectively, and may make it add a drug effect component only to some component phases.

[0018] In order that drugs may enable it to check easily by looking the condition of having separated into two or more component phases, from the capsule outside, and in order to make it make drugs divide into two or more component phases certainly, as for two or more component phases, it is desirable that all are in a liquid condition. namely, any of two or more component phases -- although -- it is desirable that it is in a liquid condition. In this case, as for each component phase, it is desirable to the shape of a layer to carry out full separation.

[0019] As equation-which-is-separable voice of each component phase, the component phase in a liquid condition will be dissociated by these two component phases according to the difference of extent of those with at least two, a hydrophilic liquid, and a hydrophobic liquid, and/or the difference of the consistency of a liquid. It is more desirable to make a component phase it not only to to use the difference of a hydrophilic property and hydrophobicity, but separate from a viewpoint of making each component phase separate certainly in the shape of a layer also using the difference of the consistency of each component phase.

[0020] Thus, in order to make it dissociate where the laminating of each drug solution is carried out by using the difference of a hydrophilic property and hydrophobicity, it can use, combining a hydrophilic liquid and a hydrophobic liquid suitably. Especially, from a viewpoint of dissociating after each drug solution has carried out the laminating certainly, polyhydric alcohol, such as a glycerol, ethylene glycol, propylene glycol, a polyethylene glycol, and a polypropylene glycol, is suitably used as a hydrophilic liquid, and a medium-chain-fatty-acid triglyceride, corn oil, soybean oil, sesame oil, etc. are suitably used as a hydrophobic liquid, for example.

[0021] On the other hand, when using the difference of a consistency, the differences of the consistency of two component phases are 0.01 g/cm<sup>3</sup>, respectively. It is 1 g/cm<sup>3</sup> above. They are 0.02 g/cm<sup>3</sup> preferably hereafter. It is 0.5 g/cm<sup>3</sup> above. It is desirable that it is the following. That is, the differences of a consistency are 0.01 g/cm<sup>3</sup>. When it is the following, it may not dissociate certainly [ each drug solution ] within a capsule, and it is 1 g/cm<sup>3</sup>. About the fault in the case of exceeding, it mentions later.

[0022] Incidentally, when an example is given, the consistency of the propylene glycol used as a hydrophilic liquid is about 1.038 g/cm<sup>3</sup> - about 1.042 g/cm<sup>3</sup>. The consistency of the medium-chain-fatty-acid triglyceride which is extent and is used as a hydrophobic liquid is about 0.94 g/cm<sup>3</sup> - about 0.96 g/cm<sup>3</sup>. It is extent and the difference is about 0.09 g/cm<sup>3</sup>. It is extent. In addition, the drugs poured into the capsule can also adjust the rate divided into each component phase using the difference of the consistency of each component phase.

[0023] Since it is comparable as an soybean, also in order to raise the visibility of a separation condition, as for the magnitude of a capsule, it is usually desirable to make it separate into two component phases, i.e., a bilayer condition, by using the drugs which contain a hydrophilic liquid and one kind of hydrophobic liquid at a time.

[0024] If each above drug solution observes the capsule separated in the shape of a layer from the

[0032] Moreover, in order to give the suitable flexibility for a capsule, it is desirable to add a glycerol into gelatin. In addition, the configuration of a capsule is not restricted to the Rugby ball shape, may be a perfect globular form and is not limited especially.

[0033] (Process) Next, how to manufacture the capsule concerning this invention is explained. The capsule concerning this invention may be manufactured by enclosing with transparency or a translucent capsule at least one component phase of the drugs which have the property divided into two or more component phases including a liquid at the time of standing at least so that the check by looking of two or more component phases formed of separation of these drugs may be attained.

[0034] At this time, it is desirable to color a component phase so that a check by looking may become easy. Moreover, it is not limited especially as an approach of enclosing drugs with a capsule, for example, the rotary method (refer to JP,57-86351,A), the seamless method, etc. are mentioned.

[0035] It is as having mentioned above about the component phases (a hydrophilic liquid, a hydrophobic liquid, a drug effect component, fine grain, etc.) contained in drugs, and these drugs contain either a hydrophilic liquid or a hydrophobic liquid at least.

[0036] Since the hydrophilic liquid and the hydrophobic liquid are mixed by homogeneity in case these drugs are poured into a capsule when using both hydrophilic liquid and hydrophobic liquid as a component phase of drugs, it is desirable to add a surfactant at drugs to extent which does not check the separation at the time of standing. If it changes into the condition that the hydrophilic liquid and hydrophobic liquid which are the component phase of drugs were mixed by homogeneity at the time of impregnation, as [ mentioned / above ], the amount of the hydrophilic liquid poured into one capsule and a hydrophobic liquid can be brought as much as possible close to the same amount, and contents can manufacture a uniform capsule.

[0037] As such a surfactant, if not harmful to the body, any of an anionic surfactant, a cationic surfactant, and an amphoteric surface active agent may be used, and it will not be limited especially. As for the amount of the surfactant used, it is desirable that it is 100 or less % of the weight 0.01 % of the weight or more on the basis of the weight (or weight of contents liquid) of the whole drugs, and it is more desirable that it is especially 50 or less % of the weight 0.02 % of the weight or more.

[0038] In addition, the difference of the consistency of each component phase (namely, a hydrophilic liquid and a hydrophobic liquid) been and divided into the liquid condition is 1 g/cm<sup>3</sup>. In exceeding Even if it uses a surfactant, drugs cannot be mixed and it cannot equalize. It compares with a hydrophobic liquid. A hydrophilic liquid is poured into a capsule remarkably superfluously, or Conversely, the balance of the hydrophilic liquid and hydrophobic liquid with which a hydrophobic liquid is poured into a capsule remarkably superfluously, and is poured into a capsule may worsen, and it may become difficult for a hydrophilic liquid and a hydrophobic liquid to produce a uniform capsule. As a component phase which is different from two or more inlets on the other hand even if it does not use a surfactant is poured in, it does not matter even if it attains equalization of two or more component phases.

[0039] It mixes so that the drugs with which it is filled up in a capsule may fully be agitated and it may become homogeneity, and after pouring in a capsule into the capsule prepared beforehand immediately, it is manufactured by sealing this capsule. After seal, if a capsule is left, a hydrophilic property, the difference of hydrophobic extent, the difference of the consistency of a liquid, the difference of the weight of a solid-state and a liquid, etc. will separate into nature and two or more component phases.

[0040] Although drugs are based also on the property of each component phase in which required time amount will be included in these drugs by the time it dissociates in the shape of a layer, by neglect, if it is left overnight, it is usually enough. In addition, time amount required for this separation can be suitably adjusted using the difference of the consistency of a liquid, as mentioned above.

[0041] (Emulsion) the drugs filled up with the above-mentioned explanation in a capsule -- two or more component phases -- dissociating -- \*\*\*\* -- two or more component phases, although there is any a component phase in a liquid condition at least It is good to replace with this, contain a hydrophilic liquid and a hydrophobic liquid as a component phase of the drugs with which it fills up in a capsule, and for these hydrophilic liquids and hydrophobic liquids able to check by looking the condition of having

dissociated in the shape of emulsion, from the capsule exterior, and also make.

[0042] If the drugs in such a condition of having emulsionized are seen from the outside of a capsule, it will be checked by looking that other component phases in a liquid condition are distributing granular in one sort of component phases in a liquid condition. Although a emulsion condition may be in the water middle-oil drop type emulsion condition that the hydrophobic liquid became a particle and has emulsionized in a hydrophilic liquid and may be in the water-in-oil-type condition that the hydrophilic liquid became a particle and has emulsionized in a hydrophobic liquid, it is desirable to have emulsionized in the state of water middle-oil drop type emulsion from a viewpoint of the stability at the time of making it dissociate in the shape of emulsion.

[0043] In addition, an emulsifier may be used if needed. Of course, it is desirable to color both a hydrophilic liquid, and hydrophobic both [ either or ] also in this emulsion, and to enable the check by looking of that emulsion condition (namely, a water-in-oil type condition or a water middle oil drop type emulsion condition) from the capsule exterior.

[0044] (Suspension) It is good for it to replace with the above emulsion conditions, and for the component phase of a liquid condition and the component phase of a solid state to be included as drugs with which it fills up in a capsule, able to make the component phase of these liquid conditions, and the component phase of a solid state able to separate in the shape of suspension, able to check by looking this condition of having made it dissociating, from the capsule exterior, and also make.

[0045] In this case, the very small thing of particle size like a fine grain and a bead as a component phase of a solid state is used. If the capsule containing such suspended drugs is seen from the outside, it will be checked by looking that the component phase in a solid state with a small particle size like a fine grain is distributing in one sort of component phases in a liquid condition.

[0046] A hydrophilic liquid and a hydrophobic liquid can be used as a component phase of the above-mentioned liquid condition. Moreover, what (or only ultralow volume is dissolved even if it dissolves) is not dissolved as a component phase of the above-mentioned solid state to a liquid like a fine grain with which it fills up in the capsule small [ particle size ] and same very much, for example is mentioned. In addition, a suspending agent may be used if needed. Of course, it is desirable to color both the component phase of a liquid condition, and component both [ either or ] of a solid state also in the case of this suspension, and to enable the check by looking of that suspension condition from the capsule exterior.

[0047] The process of the capsule from which the drugs of the above interior will be emulsionized or suspended is the same as the process of a capsule mentioned above almost. In addition, since the drugs poured in into a capsule in this case will be emulsionized or suspended beforehand, after pouring in into a capsule and sealing, it is not necessary to leave a capsule.

[0048] Since the emulsionized condition or condition of having suspended may be checked by looking from the capsule outside, it can be made to recognize to the recipe person of a capsule also in the capsule from which the drugs inside the above capsules will be emulsionized or suspended that two or more [ at least ] kinds of drug effect components are contained in a capsule. Therefore, various drug effect components are contained in the capsule concerning this invention, therefore the recipe person of this capsule thinks that the therapeutic effectiveness of the capsule concerned is high, and taking combining other chemicals beyond the need is lost.

[0049] Moreover, the drugs with which the interior is filled up can also adjust these active principles so that an incompatibility may not happen beforehand, while making each of these component phases contain a respectively different active principle, since it has separated into the condition emulsionized or suspended, i.e., two or more component phases. That is, two or more sorts of different drug effect components can be prescribed by one capsule.

[0050]

[Example] Hereafter, although this invention is explained with an example, the following examples must not be used only for the purpose of instantiation and must not be used for the purpose which limits the technical range of this invention.

[0051] (Example 1) The 1000g polyethylene glycol 400 (Nippon Oil & Fats Co., Ltd. make) was

supplied to the 5l. glass beaker. To this glass beaker, the coloring liquid which dissolved beforehand 0.1g green No. 8 coloring matter in little purified water as a coloring agent, and a 10g lauryl dimethylamino acid betaine were added, and it fully agitated to it.

[0052] Subsequently, after feeding a 1000g medium-chain-fatty-acid triglyceride (the Nippon Oil & Fats Co., Ltd. make, trade name "PANASETO P810") into the above-mentioned glass beaker, the mixture in this glass beaker was agitated for 15 minutes by about 8000 rpm using the homomixer (special machine chemically-modified company make, HV-M mold), mixture was equalized, and drugs were prepared.

[0053] Apart from this, 10kg purified gelatin (JP), 3kg concentrated glycerin (JP), and 9kg purified water were mixed, agitating, it heated to 60 degrees C and gelatin was dissolved. Next, after deaerating the air bubbles in the gelatin which dissolved, it fabricated in the shape of a sheet.

[0054] then, Rota Riidai which pours in and encloses 250mg of drugs prepared as mentioned above in that capsule while fabricating the gelatin of the shape of a sheet of two sheets in the shape of a half-segmented capsule using a capsule briquetting machine, and making this half-segmented capsule approach face to face -- the capsule by which 250mg of drugs was enclosed by law in the capsule which consists of a software capsule was manufactured.

[0055] It was made to dissociate by leaving the obtained capsule overnight, so that the laminating of a polyethylene glycol and the medium-chain-fatty-acid triglyceride may be carried out up and down. The polyethylene glycol colored green by the coloring agent was located in the lower layer, and from the capsule outside, after separation checked very easily by looking that the drugs enclosed with the capsule had separated into the polyethylene glycol and the medium-chain-fatty-acid triglyceride, and was able to carry out the thing of it. For this reason, the appearance of a capsule was very excellent.

[0056] (Example 2) The 1000g medium-chain-fatty-acid (Japanese Pharmaceutical Excipients) triglyceride (the Nippon Oil & Fats Co., Ltd. make, trade name "PANASETO P810") was fed into the 5l. glass beaker. Furthermore, hepta-oleic acid decaglyceryl was distributed by supplying 10g hepta-oleic acid decaglyceryl (Japanese surfactant company make, trade name "the deca green 7-0") to this glass beaker, and fully agitating.

[0057] Next, it added to the glass beaker and the 1000g polyethylene glycol 400 (Nippon Oil & Fats Co., Ltd. make) containing the coloring liquid which dissolved 0.1g green No. 3 coloring matter in little purified water as a coloring agent was fully agitated. Then, the mixture in this glass beaker was fully agitated for 15 minutes by about 8000 rpm using the homomixer (special machine chemically-modified company make, HV-M mold), mixture was equalized, and drugs were prepared.

[0058] Subsequently, after enclosing drugs with the capsule which consists of gelatin like an example 1, the capsule with which the 250mg of the above-mentioned drugs was enclosed was obtained by leaving it. Like the example 1, the polyethylene glycol colored green by the coloring agent was located in the lower layer, and it was also able to check this capsule by looking very easily from the capsule outside that the drugs enclosed with the capsule have separated into the polyethylene glycol and the medium-chain-fatty-acid triglyceride by looking. For this reason, the appearance of a capsule was very excellent.

[0059] (Example 3) The 1000g polyethylene glycol 400 (Nippon Oil & Fats Co., Ltd. make) was supplied to the 5l. glass beaker. To this glass beaker, the coloring liquid which dissolved beforehand 0.1g blue No. 1 coloring matter in little purified water as a coloring agent, and a 10g liquefied (JP) benzalkonium chloride were added, and it fully agitated to it.

[0060] After making it dissolve in 990g corn oil (HONEN Corporation Make) apart from this, warming 10g camphor (Nippon Fine Chemical [ Co., Ltd. ] Co., Ltd. make), mentha oil was distributed by adding 0.5 moreml mentha oil and fully agitating. Then, the mixture in this glass beaker was fully agitated for 15 minutes by about 8000 rpm using the homomixer (special machine chemically-modified company make, HV-M mold), mixture was equalized, and drugs were prepared.

[0061] Subsequently, after enclosing drugs with the capsule which consists of gelatin like an example 1, the capsule with which the 250mg of the above-mentioned drugs was enclosed was obtained by leaving it. The polyethylene glycol (salt-containing-ized benzalkonium) colored blue by the coloring agent was located in the lower layer, from the capsule outside, transparent corn oil (\*\* camphor) checked being located in the upper layer by looking very easily, and this capsule was able to carry out the thing of it.

[0062] For this reason, it has recognized filling up with the appearance of a capsule, after it not only excels very much, but the component phase which contains a benzalkonium chloride in one capsule, and the component phase containing camphor have dissociated.

[0063]

[Effect of the Invention] The capsule in this invention contains two or more kinds of active principles inside, and this capsule can make it recognize them that therapeutic effectiveness will probably be high by enabling the capsule exterior to the check by looking of the condition that the drugs with which the interior of this capsule is filled up have dissociated from the above thing to the recipe person of this capsule. Therefore, since taking combining other chemicals beyond the need is lost, the recipe person of the capsule concerning this invention can prevent an incompatibility happening.

[0064] Moreover, the drugs with which the interior is filled up can also adjust these active principles so that an incompatibility may not happen beforehand, while making each of these component phases contain a respectively different active principle, since it has separated into two or more component phases. That is, two or more sorts of active principles can be prescribed by one capsule. Moreover, the manufacture approach of the capsule in this invention can manufacture easily the capsule mentioned above.

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**MEANS**

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[Means for Solving the Problem] In the capsule which consists of drugs with which it filled up in the capsule and this capsule , it is characterize by any one component phase be in a liquid condition at least among these component phases while these drugs have separate into two or more component phases and a separation condition can check by looking the capsule concerning this invention which solves the above-mentioned technical problem from the capsule exterior .

[0007] It does not matter even if it is the hard thing currently called the hard filled capsule even if the well-known thing currently used conventionally is usable and is an elastic thing currently called the soft capsule as a capsule in the above-mentioned configuration. However, when a hard filled capsule is used, it is required to carry out a seal firmly so that the drugs containing the liquid component with which it was filled up in the capsule may not leak out of a capsule.

[0008] Moreover, as for the drugs with which it is filled up in a capsule, it is desirable that each two or more component phases which constitute these drugs are in a liquid condition, and it is more desirable to have dissociated in the shape of a layer for every component phase in this case. While it be desirable to make it separate into two or more component phases using the difference in the property of this component phase and being fastidious including the component phase which consists of a hydrophilic liquid at least, and the component phase which consists of a hydrophobic liquid, it replaces with this, and two or more component phases are the difference of the consistency of each drug solution, respectively 0.001 g/cm<sup>3</sup> It is desirable to consider as the above and to also make drugs divide into two or more component phases.

[0009] Moreover, it may be made to classify by color for every component phase. Although it is desirable to use the color of the drug effect component itself as for classification by color, it may be made to classify by color by adding the coloring agent which does not check drug effect to each component phase if needed. The above capsules may be manufactured by being filled up with the drugs with which any one component phase is in the liquid condition at least among said component phases in a capsule so that the check by looking of the condition of having separated into said two or more component phases may be attained from the outside of a capsule while separating into two or more component phases.

[0010] The capsule concerning this invention which solves the above-mentioned technical problem may be carrying out the configuration characterized by the ability of the condition of not only the gestalt separated in the shape of a layer but drugs having contained the hydrophilic liquid and the hydrophobic liquid, and this hydrophilic liquid and this hydrophobic liquid having dissociated in the shape of emulsion, and having dissociated in the shape of [ this ] emulsion to check by looking from the capsule exterior.

[0011] Moreover, the capsule concerning this invention which solves the above-mentioned technical problem may be carrying out the configuration characterized by the ability of the condition contained the component phase used as the component phase from which drugs are in the liquid condition, and a solid state, and the component phase used as the component phase which is in these liquid condition, and a solid state had dissociated in the shape of suspension, and dissociated in the shape of [ this ]

suspension to be able to check by looking from the capsule exterior.

[0012] In addition, in the above-mentioned configuration, with a component phase, you could be formed only from the drug effect component with which a capsule is filled up, and the drug effect component was dissolved in the solvent, and it could be formed, and is not especially limited.

[0013]

[Embodiment of the Invention] Hereafter, the gestalt of 1 operation of this invention is explained to a detail. Even if there are few two or more component phases, the drugs with which the interior of the capsule in the gestalt of this operation is filled up have any one component phase in a liquid condition, while having separated into two or more component phases within a capsule.

[0014] In the case of the component phase in a liquid condition, as long as it is the liquid which does not dissolve a capsule as a solvent which dissolves a drug effect component, even if it is which liquid, it can use regardless of whether it is a hydrophilic property or it is hydrophobicity. As a hydrophilic liquid, polyhydric alcohol, such as lower alcohol, such as ethanol, a glycerol, glycetyl triacetate, ethylene glycol, propylene glycol, a polyethylene glycol, and a polypropylene glycol, isomerization honeydew, the liquid surfactant of a hydrophilic property, the thing that combined these are mentioned, for example.

[0015] On the other hand, as a hydrophobic liquid, triglycerides, such as a medium-chain-fatty-acid triglyceride, corn oil, olive oil, safflower oil, cotton seed oil, sesame oil, soybean oil, oleum rapae, peanut oil, palm oil, sunflower oil, jojoba oil, the poppy oil, a liquid paraffin, an oleophilic oily surfactant, the thing that combined these are mentioned.

[0016] Moreover, especially as a drug effect component which dissolves in a hydrophilic liquid, although not limited, a benzalkonium chloride, water soluble vitamin, an antipyrin, chlorpromazine hydrochloride, diphenhydramine hydrochloride, naphazoline hydrochloride, guaifenesin, sodium salicylate, dextromethorphan hydrobromide, chlorpheniramine maleate, acetaminophen, caffeine, dl-methylephedrine hydrochloride, dihydrocodeine phosphate, diprophylline, etc. are mentioned, for example.

[0017] On the other hand, especially as a drug effect component which dissolves in a hydrophobic liquid, although not limited, camphor, fat soluble vitamin, liver oil, a borneol, metenolone acetate, ibuprofen, isopropylantipyrine, ethenzamide, etc. are mentioned, for example. Moreover, you may make it add to each component phase, respectively, and may make it add a drug effect component only to some component phases.

[0018] In order that drugs may enable it to check easily by looking the condition of having separated into two or more component phases, from the capsule outside, and in order to make it make drugs divide into two or more component phases certainly, as for two or more component phases, it is desirable that all are in a liquid condition. namely, any of two or more component phases -- although -- it is desirable that it is in a liquid condition. In this case, as for each component phase, it is desirable to the shape of a layer to carry out full separation.

[0019] As equation-which-is-separable voice of each component phase, the component phase in a liquid condition will be dissociated by these two component phases according to the difference of extent of those with at least two, a hydrophilic liquid, and a hydrophobic liquid, and/or the difference of the consistency of a liquid. It is more desirable to make a component phase it not only to use the difference of a hydrophilic property and hydrophobicity, but separate from a viewpoint of making each component phase separate certainly in the shape of a layer also using the difference of the consistency of each component phase.

[0020] Thus, in order to make it dissociate where the laminating of each drug solution is carried out by using the difference of a hydrophilic property and hydrophobicity, it can use, combining a hydrophilic liquid and a hydrophobic liquid suitably. Especially, from a viewpoint of dissociating after each drug solution has carried out the laminating certainly, polyhydric alcohol, such as a glycerol, ethylene glycol, propylene glycol, a polyethylene glycol, and a polypropylene glycol, is suitably used as a hydrophilic liquid, and a medium-chain-fatty-acid triglyceride, corn oil, soybean oil, sesame oil, etc. are suitably used as a hydrophobic liquid, for example.

[0021] On the other hand, when using the difference of a consistency, the differences of the consistency of two component phases are 0.01 g/cm<sup>3</sup>, respectively. It is 1 g/cm<sup>3</sup> above. They are 0.02 g/cm<sup>3</sup> preferably hereafter. It is 0.5 g/cm<sup>3</sup> above. It is desirable that it is the following. That is, the differences of a consistency are 0.01 g/cm<sup>3</sup>. When it is the following, it may not dissociate certainly [ each drug solution ] within a capsule, and it is 1 g/cm<sup>3</sup>. About the fault in the case of exceeding, it mentions later.

[0022] Incidentally, when an example is given, the consistency of the propylene glycol used as a hydrophilic liquid is about 1.038 g/cm<sup>3</sup> - about 1.042 g/cm<sup>3</sup>. The consistency of the medium-chain-fatty-acid triglyceride which is extent and is used as a hydrophobic liquid is about 0.94 g/cm<sup>3</sup> - about 0.96 g/cm<sup>3</sup>. It is extent and the difference is about 0.09 g/cm<sup>3</sup>. It is extent. In addition, the drugs poured into the capsule can also adjust the rate divided into each component phase using the difference of the consistency of each component phase.

[0023] Since it is comparable as an soybean, also in order to raise the visibility of a separation condition, as for the magnitude of a capsule, it is usually desirable to make it separate into two component phases, i.e., a bilayer condition, by using the drugs which contain a hydrophilic liquid and one kind of hydrophobic liquid at a time.

[0024] If each above drug solution observes the capsule separated in the shape of a layer from the outside, it will be checked by looking that one sort of drug solutions in a liquid condition and other drug solutions in a liquid condition dissociated up and down, a drug solution with a more low consistency separates into the upper part inside a capsule, and the drug solution with a more high consistency has separated into the lower part inside a capsule.

[0025] Although each drugs divided into two or more component phases suited the liquid condition in old explanation, in this invention, other component phases may be in a solid state that there should just be at least one component phase in a liquid condition among two or more separated component phases. In this case, as a component phase in a solid state, what has a usually very small particle size like a fine grain is used. That is, by using a hydrophobic liquid and the fine grain which has a high hydrophilic property, using a hydrophilic liquid and the fine grain which has high hydrophobicity, it is made to separate into a liquid and a fine grain, and this separation condition is good also as the capsule exterior to a check by looking being possible. Of course, a drug effect component may be included in a fine grain in this case.

[0026] As mentioned above, since the drugs with which the interior is filled up can check by looking the condition of having separated into two or more component phases, from the capsule outside, it can be made to recognize to the recipe person of a capsule in the capsule concerning this invention that two or more [ at least ] kinds of drug effect components are contained in a capsule. Therefore, various drug effect components are contained in the capsule concerning this invention, therefore the recipe person of this capsule thinks that the therapeutic effectiveness of the capsule concerned is high, and what it is going to take combining other chemicals beyond the need is lost. That is, a capsule recipe person needs to cease to do the method of medicinal recipe which causes an incompatibility by taking the capsule concerning this invention.

[0027] Moreover, the drugs with which the interior is filled up can also adjust these drug effect components so that an incompatibility may not happen beforehand, while making each of these component phases contain a respectively different drug effect component, since it has separated into two or more component phases. That is, two or more sorts of drug effect components can be safely prescribed by one capsule.

[0028] You may make it classify two or more component phases divided into any one component phase using the colored thing at least among two or more separated component phases by color in the capsule concerning this invention. It is not limited, but the solvent which dissolves a drug effect component also besides the drug effect component which forms the component phase itself using a colored thing may use a colored thing, and you may make it add a coloring agent in the component phase of a liquid condition especially as a means which makes a component phase colored at this time. In addition, when a coloring agent is used, it is desirable to make it dissolve in the solvent of pole small quantity, and to pre-use a coloring agent as coloring liquid.

[0029] Moreover, when a solid-state and liquids, such as a fine grain, are put together, solid-states, such as a fine grain, may be colored, or you may be colorlessness, and a liquid may be colored, or you may be colorlessness. Thus, if any one component phase serves as a color of the drugs divided into two or more component phases which can be checked by looking from the capsule exterior at least, when it will become very easy to check separation to two or more component phases of drugs by looking from the capsule outside, the appearance of a capsule is also excellent, and appearance can obtain a good capsule.

[0030] Furthermore, according to the class of drug effect component in a component phase, when classification by color is made, the affinity of component phases can be known at a glance, and a medical practitioner and a pharmacist can also check by looking whether the recipe person of a capsule contains the component phase whose body of his the drugs with which it fills up in the capsule not to mention the incompatibility do not suit from the first.

[0031] As a charge of a principal member which forms the capsule of the capsule concerning this invention, it has a suitable degree of hardness, the interior of a capsule can be made transparently possible [ a check by looking ] or translucent, and, moreover, gelatin with easy shaping is used for the form of arbitration. The capsule is formed in the Rugby ball shape of gelatin.

[0032] Moreover, in order to give the suitable flexibility for a capsule, it is desirable to add a glycerol into gelatin. In addition, the configuration of a capsule is not restricted to the Rugby ball shape, may be a perfect globular form and is not limited especially.

[0033] (Process) Next, how to manufacture the capsule concerning this invention is explained. The capsule concerning this invention may be manufactured by enclosing with transparency or a translucent capsule at least one component phase of the drugs which have the property divided into two or more component phases including a liquid at the time of standing at least so that the check by looking of two or more component phases formed of separation of these drugs may be attained.

[0034] At this time, it is desirable to color a component phase so that a check by looking may become easy. Moreover, it is not limited especially as an approach of enclosing drugs with a capsule, for example, the rotary method (refer to JP,57-86351,A), the seamless method, etc. are mentioned.

[0035] It is as having mentioned above about the component phases (a hydrophilic liquid, a hydrophobic liquid, a drug effect component, fine grain, etc.) contained in drugs, and these drugs contain either a hydrophilic liquid or a hydrophobic liquid at least.

[0036] Since the hydrophilic liquid and the hydrophobic liquid are mixed by homogeneity in case these drugs are poured into a capsule when using both hydrophilic liquid and hydrophobic liquid as a component phase of drugs, it is desirable to add a surfactant at drugs to extent which does not check the separation at the time of standing. If it changes into the condition that the hydrophilic liquid and hydrophobic liquid which are the component phase of drugs were mixed by homogeneity at the time of impregnation, as [ mentioned / above ], the amount of the hydrophilic liquid poured into one capsule and a hydrophobic liquid can be brought as much as possible close to the same amount, and contents can manufacture a uniform capsule.

[0037] As such a surfactant, if not harmful to the body, any of an anionic surfactant, a cationic surfactant, and an amphoteric surface active agent may be used, and it will not be limited especially. As for the amount of the surfactant used, it is desirable that it is 100 or less % of the weight 0.01 % of the weight or more on the basis of the weight (or weight of contents liquid) of the whole drugs, and it is more desirable that it is especially 50 or less % of the weight 0.02 % of the weight or more.

[0038] In addition, the difference of the consistency of each component phase (namely, a hydrophilic liquid and a hydrophobic liquid) been and divided into the liquid condition is 1 g/cm<sup>3</sup>. In exceeding Even if it uses a surfactant, drugs cannot be mixed and it cannot equalize. It compares with a hydrophobic liquid. A hydrophilic liquid is poured into a capsule remarkably superfluously, or Conversely, the balance of the hydrophilic liquid and hydrophobic liquid with which a hydrophobic liquid is poured into a capsule remarkably superfluously, and is poured into a capsule may worsen, and it may become difficult for a hydrophilic liquid and a hydrophobic liquid to produce a uniform capsule. As a component phase which is different from two or more inlets on the other hand even if it does not

use a surfactant is poured in, it does not matter even if it attains equalization of two or more component phases.

[0039] It mixes so that the drugs with which it is filled up in a capsule may fully be agitated and it may become homogeneity, and after pouring in a capsule into the capsule prepared beforehand immediately, it is manufactured by sealing this capsule. After seal, if a capsule is left, a hydrophilic property, the difference of hydrophobic extent, the difference of the consistency of a liquid, the difference of the weight of a solid-state and a liquid, etc. will separate into nature and two or more component phases.

[0040] Although drugs are based also on the property of each component phase in which required time amount will be included in these drugs by the time it dissociates in the shape of a layer, by neglect, if it is left overnight, it is usually enough. In addition, time amount required for this separation can be suitably adjusted using the difference of the consistency of a liquid, as mentioned above.

[0041] (Emulsion) the drugs filled up with the above-mentioned explanation in a capsule -- two or more component phases -- dissociating -- \*\*\*\* -- two or more component phases, although there is any a component phase in a liquid condition at least It is good to replace with this, contain a hydrophilic liquid and a hydrophobic liquid as a component phase of the drugs with which it fills up in a capsule, and for these hydrophilic liquids and hydrophobic liquids able to check by looking the condition of having dissociated in the shape of emulsion, from the capsule exterior, and also make.

[0042] If the drugs in such a condition of having emulsionized are seen from the outside of a capsule, it will be checked by looking that other component phases in a liquid condition are distributing granular in one sort of component phases in a liquid condition. Although a emulsion condition may be in the water middle-oil drop type emulsion condition that the hydrophobic liquid became a particle and has emulsionized in a hydrophilic liquid and may be in the water-in-oil-type condition that the hydrophilic liquid became a particle and has emulsionized in a hydrophobic liquid, it is desirable to have emulsionized in the state of water middle-oil drop type emulsion from a viewpoint of the stability at the time of making it dissociate in the shape of emulsion.

[0043] In addition, an emulsifier may be used if needed. Of course, it is desirable to color both a hydrophilic liquid, and hydrophobic both [ either or ] also in this emulsion, and to enable the check by looking of that emulsion condition (namely, a water-in-oil type condition or a water middle oil drop type emulsion condition) from the capsule exterior.

[0044] (Suspension) It is good for it to replace with the above emulsion conditions, and for the component phase of a liquid condition and the component phase of a solid state to be included as drugs with which it fills up in a capsule, able to make the component phase of these liquid conditions, and the component phase of a solid state able to separate in the shape of suspension, able to check by looking this condition of having made it dissociating, from the capsule exterior, and also make.

[0045] In this case, the very small thing of particle size like a fine grain and a bead as a component phase of a solid state is used. If the capsule containing such suspended drugs is seen from the outside, it will be checked by looking that the component phase in a solid state with a small particle size like a fine grain is distributing in one sort of component phases in a liquid condition.

[0046] A hydrophilic liquid and a hydrophobic liquid can be used as a component phase of the above-mentioned liquid condition. Moreover, what (or only ultralow volume is dissolved even if it dissolves) is not dissolved as a component phase of the above-mentioned solid state to a liquid like a fine grain with which it fills up in the capsule small [ particle size ] and same very much, for example is mentioned. In addition, a suspending agent may be used if needed. Of course, it is desirable to color both the component phase of a liquid condition, and component both [ either or ] of a solid state also in the case of this suspension, and to enable the check by looking of that suspension condition from the capsule exterior.

[0047] The process of the capsule from which the drugs of the above interior will be emulsionized or suspended is the same as the process of a capsule mentioned above almost. In addition, since the drugs poured in into a capsule in this case will be emulsionized or suspended beforehand, after pouring in into a capsule and sealing, it is not necessary to leave a capsule.

[0048] Since the emulsionized condition or condition of having suspended may be checked by looking

from the capsule outside, it can be made to recognize to the recipe person of a capsule also in the capsule from which the drugs inside the above capsules will be emulsionized or suspended that two or more [ at least ] kinds of drug effect components are contained in a capsule. Therefore, various drug effect components are contained in the capsule concerning this invention, therefore the recipe person of this capsule thinks that the therapeutic effectiveness of the capsule concerned is high, and taking combining other chemicals beyond the need is lost.

[0049] Moreover, the drugs with which the interior is filled up can also adjust these active principles so that an incompatibility may not happen beforehand, while making each of these component phases contain a respectively different active principle, since it has separated into the condition emulsionized or suspended, i.e., two or more component phases. That is, two or more sorts of different drug effect components can be prescribed by one capsule.

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[Translation done.]

**\* NOTICES \***

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1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. \*\*\*\* shows the word which can not be translated.
3. In the drawings, any words are not translated.

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**EXAMPLE**

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[Example] Hereafter, although this invention is explained with an example, the following examples must not be used only for the purpose of instantiation and must not be used for the purpose which limits the technical range of this invention.

[0051] (Example 1) The 1000g polyethylene glycol 400 (Nippon Oil & Fats Co., Ltd. make) was supplied to the 5l. glass beaker. To this glass beaker, the coloring liquid which dissolved beforehand 0.1g green No. 8 coloring matter in little purified water as a coloring agent, and a 10g lauryl dimethylamino acid betaine were added, and it fully agitated to it.

[0052] Subsequently, after feeding a 1000g medium-chain-fatty-acid triglyceride (the Nippon Oil & Fats Co., Ltd. make, trade name "PANASETO P810") into the above-mentioned glass beaker, the mixture in this glass beaker was agitated for 15 minutes by about 8000 rpm using the homomixer (special machine chemically-modified company make, HV-M mold), mixture was equalized, and drugs were prepared.

[0053] Apart from this, 10kg purified gelatin (JP), 3kg concentrated glycerin (JP), and 9kg purified water were mixed, agitating, it heated to 60 degrees C and gelatin was dissolved. Next, after deaerating the air bubbles in the gelatin which dissolved, it fabricated in the shape of a sheet.

[0054] then, Rota Riidai which pours in and encloses 250mg of drugs prepared as mentioned above in that capsule while fabricating the gelatin of the shape of a sheet of two sheets in the shape of a half-segmented capsule using a capsule briquetting machine, and making this half-segmented capsule approach face to face -- the capsule by which 250mg of drugs was enclosed by law in the capsule which consists of a software capsule was manufactured.

[0055] It was made to dissociate by leaving the obtained capsule overnight, so that the laminating of a polyethylene glycol and the medium-chain-fatty-acid triglyceride may be carried out up and down. The polyethylene glycol colored green by the coloring agent was located in the lower layer, and from the capsule outside, after separation checked very easily by looking that the drugs enclosed with the capsule had separated into the polyethylene glycol and the medium-chain-fatty-acid triglyceride, and was able to carry out the thing of it. For this reason, the appearance of a capsule was very excellent.

[0056] (Example 2) The 1000g medium-chain-fatty-acid (Japanese Pharmaceutical Excipients) triglyceride (the Nippon Oil & Fats Co., Ltd. make, trade name "PANASETO P810") was fed into the 5l. glass beaker. Furthermore, hepta-oleic acid decaglyceryl was distributed by supplying 10g hepta-oleic acid decaglyceryl (Japanese surfactant company make, trade name "the deca green 7-0") to this glass beaker, and fully agitating.

[0057] Next, it added to the glass beaker and the 1000g polyethylene glycol 400 (Nippon Oil & Fats Co., Ltd. make) containing the coloring liquid which dissolved 0.1g green No. 3 coloring matter in little purified water as a coloring agent was fully agitated. Then, the mixture in this glass beaker was fully agitated for 15 minutes by about 8000 rpm using the homomixer (special machine chemically-modified company make, HV-M mold), mixture was equalized, and drugs were prepared.

[0058] Subsequently, after enclosing drugs with the capsule which consists of gelatin like an example 1, the capsule with which the 250mg of the above-mentioned drugs was enclosed was obtained by leaving it. Like the example 1, the polyethylene glycol colored green by the coloring agent was located in the

lower layer, and it was also able to check this capsule by looking very easily from the capsule outside that the drugs enclosed with the capsule have separated into the polyethylene glycol and the medium-chain-fatty-acid triglyceride by looking. For this reason, the appearance of a capsule was very excellent.

[0059] (Example 3) The 1000g polyethylene glycol 400 (Nippon Oil & Fats Co., Ltd. make) was supplied to the 5l. glass beaker. To this glass beaker, the coloring liquid which dissolved beforehand 0.1g blue No. 1 coloring matter in little purified water as a coloring agent, and a 10g liquefied (JP) benzalkonium chloride were added, and it fully agitated to it.

[0060] After making it dissolve in 990g corn oil (HONEN Corporation Make) apart from this, warming 10g camphor (Nippon Fine Chemical [ Co., Ltd. ] Co., Ltd. make), mentha oil was distributed by adding 0.5 moreml mentha oil and fully agitating. Then, the mixture in this glass beaker was fully agitated for 15 minutes by about 8000 rpm using the homomixer (special machine chemically-modified company make, HV-M mold), mixture was equalized, and drugs were prepared.

[0061] Subsequently, after enclosing drugs with the capsule which consists of gelatin like an example 1, the capsule with which the 250mg of the above-mentioned drugs was enclosed was obtained by leaving it. The polyethylene glycol (salt-containing-ized benzalkonium) colored blue by the coloring agent was located in the lower layer, from the capsule outside, transparent corn oil (\*\* camphor) checked being located in the upper layer by looking very easily, and this capsule was able to carry out the thing of it.

[0062] For this reason, it has recognized filling up with the appearance of a capsule, after it not only excels very much, but the component phase which contains a benzalkonium chloride in one capsule, and the component phase containing camphor have dissociated.

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[Translation done.]